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# Synthesis of 4-Amino-5-furyl-2-yl-4H-1, 2, 4-triazole-3-thiol Derivatives as a Novel Class of Endothelin(ET) Receptor Antagonists

Xin Yong LIU*, Wen Fang XU, Jing De WU

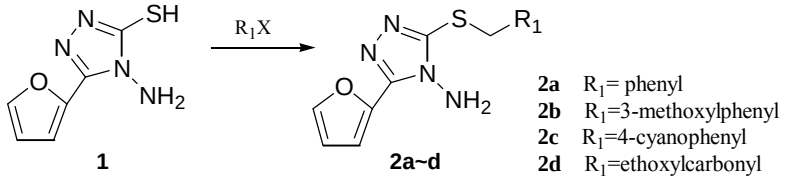
School of Pharmacy, Shandong University, Jinan 250012

**Abstract:** A series of novel 3-alkylthio-4-arylideneamino-5-(2-furyl)-1, 2, 4-triazole derivatives were synthesized. Their chemical structures were confirmed with elemental analysis and spectral data. Endothelin(ET) receptor competitive binding assay showed that some compounds exhibited high selective as potent ET-1 receptor antagonist.

**Keywords:** 1, 2, 4-Triazole derivatives, ET antagonist.

Endothelin(ET), as a peptides family secreted from endothelial cell, plays a very important physiological role in vasoconstraction, and ET receptor antagonists attract much attention in search for novel therapeutics for the various cardiovascular diseases (CVDs)[1]. 1, 2, 4-Triazole derivatives have been widely investigated due to their broad spectrum of pharmacological activities, such as antitumor[2], antiviral[3], antibacterial[4,5], antifungal[6], anti-inflammatory[7], analgesic[8] and antidepressant[9]. 4-Substituted amino or 3-alkylated sulfanyl-1, 2, 4-triazole derivatives were synthesized and found to be an active antibacterial agents in our previous work[10]. However, some 3-alkylthio- 4-arylideneamino-5-(2-furyl)-1, 2, 4-triazoles have not been reported so far. Prompted by these observations and in continuing our work on biologically study of 1, 2, 4-triazole heterocycles, herein we reported the synthesis and pharmacological evaluation of the new 3, 4, 5-trisubstituted-1, 2, 4-triazole derivatives as a novel class of ET receptor antagonists.

**Scheme 1**




**1** **2a~d**

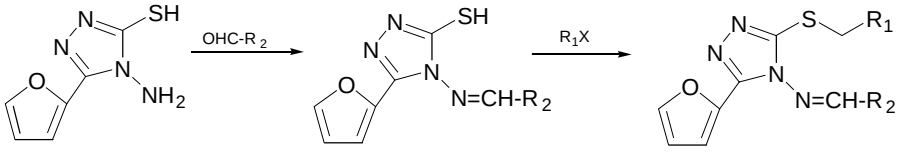
**2a** $R_1$= phenyl
**2b** $R_1$=3-methoxylphenyl
**2c** $R_1$=4-cyanophenyl
**2d** $R_1$=ethoxylcarbonyl

*E-mail:xinyongl@jn-public.sd.cninfo.net

Compound **1,** 4-amino-5-(2-furyl)-4H-1, 2, 4-triazole-3-thiol, was prepared according to literature[10]. Compounds **2** were prepared by the alkylation of compound **1** with alkyl halide in potassium hydroxide ethanol solution (**Scheme 1**). Schiff bases **3** were obtained by the condensation of compound **1** with different aldehydes under refluxing in ethanol solution. The S-alkylation reaction of the compounds **3** was carried out in the similar manner as the preparation of compounds **2** to obtain compounds **4 (Scheme 2)**.

The structures of all synthesized compounds were confirmed on the basis of elemental analysis, $^1$HNMR and IR spectra.

**Scheme 2**




**1** **3a~b** **4a~e**

**3a** $R_2$=2-nitrofuryl
**3b** $R_2$=3,5-dimethylphenyl

| | $R_1$ | $R_2$ |
|---|---|---|
| **4a** | phenyl | 2-nitrofuryl |
| **4b** | 3-methoxyphenyl | 2-nitrofuryl |
| **4c** | 4-cynophenyl | 2-nitrofuryl |
| **4d** | ethoxycarbonyl | 2-nitrofuryl |
| **4e** | phenyl | 3,4-dimethoxylphenyl |
| **4f** | ethoxylcarbonyl | 3,4-dimethoxylphenyl |

*Synthesis of 4-(5-nitrofurylidene)amino-5-(2-furyl)-1, 2, 4-triazole-3-thiol **3a***

Compound **1**(0.1 mmol) was refluxed with 5-nitro-2-furaldehyde diacetate in sulfuric acid, ethanol and water (0.1:1:2) solution for 2 h, and recrystallized from acetone/ ethanol (4:1), yellow needles, yield 98.3%, mp:198~201°C. $^1$HNMR (DMSO-$d_6$) δ ppm: 14.39(s, 1H, NH or SH); 10.34(s, 1H, -N=CH), 8.01(d, 1H, J=1.5Hz, furan H-5'); 7.88(d, 1H, AB, $J_1$=3.5Hz, furan H-4″); 7.75(d, 1H, AB, $J_2$=3.5Hz, furan H-3″); 7.28(d, 1H, J=3.0Hz, furan H-3'); 6.78(dd, 1H, $J_1$=1.5 Hz, $J_2$=3.0 Hz, furan H-4′). IR(KBr, $cm^{-1}$): 3109（s, $\upsilon_{=CH}$）, 2977,2936（w, $\upsilon_{CH}$）, 1623（s, $\upsilon_{C=N}$）, 1536 (s, $\upsilon as_{NO2}$), 1450(s, $\upsilon_{C=C}$), 1349(s, $\upsilon_{NO2,}$), 1274(s, $\upsilon_{N-N=C}$), 968(s), 721(m, $\upsilon_{C-S-C}$).

*Synthesis of 4-(3,4-dimethoxylphenylidene)amino-5-(2-furyl)-1,2,4-triazole-3-thiol **3b***

Compound **1** (0.1 mmol) was refluxed with 3,4-dimethoxylphenyl aldehyde (0.11 mmol) for 3 h. **3b** was recrystallized from ethanol as white needles. yield 56.1%, mp: 225~227°C. IR(KBr, $cm^{-1}$): 3137, 3115(m, $\nu_{Ar-H}$), 2963, 2933($\nu_{CH3}$), 1604($\nu_{C=C}$), 1275(m, $\nu_{N-N=C}$). Anal. calcd. For $C_{15}H_{14}N_4O_3S$(%): C 54.54, H 4.27, N 16.96. Found: C 54.27, H 4.13, N 17.03.

*General procedure for the preparation of compounds **2** or **4***

A suspension of **1** or **3**(1 mmol) in 10 mL of ethanol was added dropwise 1 mL of KOH water solution (2 $mol.L^{-1}$) in cooling and with vigorous stirring. While the solid was

dissolved, alkyl halide (1.2 mmol) was added dropwise. After addition, the temperature was kept at 25°C for 1-2 h, then the reaction mixture was cooled, the white precipitate was filtered, recrystallized from proper solvent.

*3-Benzylthio-4-(5-nitrofurylidene)amino-5-(2-furyl)-1,2,4-triazole* ***4a***

Recrystallized from ethanol, yellow needles, yield 66.4%, mp:159~161°C. $^1$HNMR (DMSO-$d_6$) δ ppm: 8.82(s, 1H, -N=CH), 7.93(d, 1H, J=1.5Hz, furan H-5'), 7.83(d, 1H, AB, $J_1$=3.6Hz, furan H-4″), 7.65(d, 1H, AB, $J_2$=3.6Hz, furan H-3″), 7.34~7.22 (m, 5H, Ph-H), 7.02(d, 1H, J=3.6Hz, furan H-3′), 6.71(dd, 1H, $J_1$=1.5 Hz, $J_2$=3.6Hz, furan H-4′), 4.43(s, 1H, $SCH_2$). IR(KBr, $cm^{-1}$): 3123, 3027(w, Ar-H); 1572, 1495, 1435, 1347(s), 1275, 1255, 1014, 964, 743, 710. Anal. calcd. for $C_{15}H_{14}N_4O_3S$ (%): C 54.68, H 3.31, N 17.71. Found: C 54.80, H 3.35, N 17.85.

*3-(3-Methoxybenzyl)thio-4-(5-nitrofurylidene)amino-5-(2-furyl)-1,2,4-triazole* ***4b***

Separated by flash column chromatography(FCC) using eluent cyclohexane/ethyl acetate(1:3), and recrystallizaed from ethanol/petroleum ether (bp:90°C), yellow needles, yield 49.2%, mp:77~79°C. $^1$HNMR(DMSO-$d_6$) δ ppm: 8.82(s, 1H, =CH), 7.93(d, 1H, J=1.5Hz, furan H-5′), 7.84(d, 1H, J=4.0Hz, furan H-3″), 7.64(d, 1H, J=4.0Hz, furan H-4′), 7.16(m, 1H, Ph-H), 7.01(d, 1H, J=3.6Hz, furan H-3'), 6.87~6.82 (m, 3H, Ph-H), 6.70(dd, 1H, $J_1$=1.5Hz, $J_2$=3.6Hz, furan H-4′), 4.37(s, 2H, $SCH_2$), 3.65(s, 3H, $OCH_3$). IR(KBr, $cm^{-1}$): 3091(s, $\nu_{Ar-H}$), 1532, 1492, 1441, 1349(s), 1267, 967. Anal. calcd. for $C_{15}H_{14}N_4O_3S$(%): C 53.52, H 3.78, N 16.42. Found: C 52.82, H 3.85, N 17.01.

*3-(4-Cyanobenzyl)thio-4-(5-nitrofurylidene)amino-5-(2-furyl)-1,2,4-triazole* ***4c***

Recrystallized from ethanol, yellow needles, yield 78%, mp: 207~209°C. $^1$HNMR (DMSO-$d_6$) δ ppm: 8.85(s, 1H, =CH), 7.92(d, 1H, J=1.5Hz, furan H-5′), 7.84(d, 1H, J=4.0Hz, furan H-4″), 7.73(d, 2H, J=8.2Hz, Ph 2,6-2H), 7.65(d, 1H, J=4.0Hz, furan H-3″), 7.52(d, 2H, J=8.2Hz, Ph 3,5-2H), 7.01(d, 1H, J=3.6Hz, furan H-3′), 6.70(dd, 1H, $J_1$=1.5Hz, $J_2$=3.6 Hz, furan H-4′), 4.48(s, 1H, $SCH_2$). IR(KBr, $cm^{-1}$): 2226($\nu_{CN}$), 1531, 1436, 1349, 1272, 1021, 965, 810, 754, 738. Anal. calcd. for $C_{19}H_{12}N_6O_4S$(%): C 54.28, H 2.88, N 19.99. Found: C 54.40, H 2.95, N 20.10.

*3-(Ethoxycarbonyl)methylthio-4-(5-nitrofurylidene)amino-5-(2-furyl)-1,2,4-triazol* ***4d***

Recrystallized from ethanol, yellow needles, yield 80%, mp:127~129°C. $^1$HNMR (DMSO-$d_6$) δ ppm: 8.94(s, 1H, =CH), 7.93(d, 1H, J= 1.5 Hz, furan H-5'), 7.86(d, 1H, J=3.6Hz, furan H-4″), 7.71(d, 1H, J=3.6Hz, furan H-3″), 7.06(d, 1H, J=3.0Hz, furan H-3′), 6.72(dd, 1H, $J_1$=1.5Hz, $J_2$=3.Hz, furan H-4′), 4.08(q, 2H, J=7.2Hz, $OCH_2$), 4.07(s, 2H, $SCH_2$), 1.13(t, 3H, J=7.2Hz, $CH_3$). IR (KBr, $cm^{-1}$): 1736(s, $\nu_{C=O}$), 1530, 1442, 1349, 1307, 1278, 1188, 1028, 766. Anal. calcd. for $C_{15}H_{13}N_5O_6S$(%): C 46.04, H 3.35, N 17.89. Found: C45.87, H 3.39, N 18.08.

*3-(2-Furyl)-4-(3,4-dimethoxyphenylidene)amino-5-benzylthio-1, 2, 4-triazole* ***4e***

Separated by FCC, eluented with hexane/ethyl acetate(3:2), and recrystallized from ethanol, white crystals. yield 48.1%, mp:100~102°C. IR(KBr, $cm^{-1}$): 3100（$\nu_{=CH}$）; 3025 (Ph-H), 2957, 2935($\nu_{CH3}$), 1598, 1576, 1513(s), 1274 (s, $\nu_{N-N=C}$), 1138(s), 1026, 1020(s); 784, 704($\nu_{C-S-C}$). Anal. calcd. for $C_{22}H_{20}N_4O_3S$(%): C 62.84, H 4.79, N 13.32. Found: C62.96, H 4.83, N 13.28.

*3-(Ethoxycarbonyl)methylthio-4-(3,4-dimethoxyphenylidene)amino-5-(2-furyl)-1,2,4-triazole* ***4f***

Recrystllized from acetone/cyclohexane(1:1), white crystals. yield 33.4%, mp:196~199°C. $^1$HNMR(DMSO-$d_6$) δ ppm: 8.62(s, 1H, =CH), 7.89(d, 1H, J=1.5Hz, furan H-5'), 7.31(m, 1H, Ph-H), 7.22(d, 1H, J=3.0Hz, furan H-3'), 7.01~6.86(m, 2H, Ph-H), 6.68(dd, 1H, $J_1$=1.5Hz, $J_2$=3.0Hz, furan H-4′), 4.91(s, 2H, $SCH_2$), 4.13(q, 2H, J=7.2Hz, $OCH_2$), 3.69(s, 3H, $OCH_3$), 3.57(s, 3H, $OCH_3$), 1.13(t, 3H, J=7.2Hz, $CH_3$).

ET receptor competitive binding assay was tested in the cell culture solution of the rat heart ventricle muscle membranes. Bosentan, an $ET_{A/B}$ receptor antagonist, was selected as positive standard, and [$^{125}$I]ET-1 was used as ET receptor radioligand. The results are listed in **Table 1**. Compound **3a** exhibited high inhibition of 71.93%, and represented a new leading compound of ET receptor antagonist for further study.

**Table 1** The results of ET receptor competitive binding assay of the compounds **1, 2, 3** and **4**

| Compounds No. | **1** | **2a** | **2b** | **3a** | **4a** | **4b** | **4d** | **4e** | **4f** |
|---|---|---|---|---|---|---|---|---|---|
| Inhibition (%)[a] | 16.9 | -67.96[b] | -50.24 | 71.93 | 32.76 | -98.74 | 11.3 | 15.9 | 7.58 |

[a]The final concentration of tested compounds was $10^{-2}$mg/mL. [b]Negative values have no any real meaning.

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